

Amendments to the Specification:

Please cancel the paragraph beginning at page 8, line 1.

Please replace the paragraph beginning at page 8, line 2, with the following paragraph:

--Figure [[2]]1. The detection efficiency of various PEO polymers in ESI-TOF.--

Please replace the paragraph beginning at page 8, line 3, with the following paragraph:

--Figure [[3]]2. PEO monomer detection efficiency as a function of weight fraction.--

Please cancel the paragraph beginning at page 8, line 4.

Please cancel the paragraph beginning at page 8, line 5.

Please replace the paragraph beginning at page 9, line 5, with the following paragraph:

--The critical question in MS is where do all the molecules go? Using an electrospray time-of-flight (ESI-TOF) MS as an example (**Figure 1**), it is obvious that there are many possibilities for ion loss. Molecules may fail to ionize in the first place, or they could form net neutral salts with entrained counterions on desolvation in ESI (Kebarle, P., *J Mass Spectrom.*, 35:804-817 (2000)) or through coupled volatilization of the analyte-salt matrix in MALDI. Ions may fail to enter the detector orifice. Micro/nanospray techniques tremendously improved the collection efficiency in ESI MS over the previous pneumatic spray technology. The inner surfaces of the MS are maintained at different potentials to create electric fields that both contain the ions while they are separated from neutral gas molecules and direct the ions to the detection element. Ions may be lost to electrostatic interactions with the inner surfaces of the MS. The MS detector must operate at high vacuum so that the mean free path of the ions to the detector element is long enough that the ion trajectory depends only on the intrinsic mass to charge of the ion itself. Therefore, some ions may be entrained in the neutral gases being removed to the vacuum pump. An orthogonal ion detector, ~~is shown in Figure 1 which results may result~~ in additional ion losses due to the intrinsic duty cycle of the detector.--

Please replace the paragraph beginning at page 13, line 3, with the following paragraph:

--A great deal of effort has already gone into the optimization of ion transmission inside the detector, with zmol ion efficiencies being achieved even through tandem MS detectors. (Belov, M.E. et al., *Anal. Chem.*, 72:2271-2279 (2000)). This high transmission efficiency is readily demonstrated by a few simple experiments. Collection efficiency can be tested by the use of a low pressure ESI head (**Figure 4**), simplified from that described by Karger. (Felton, C., et al., *Anal. Chem.*, 73:1449-1454 (2000)). Because the ESI source and nozzle are sealed from the

atmosphere, all gas phase ions created at the spray tip must enter the mass analyzer. The diameter and length of the capillary are manipulated to alter the sample flow rate under vacuum. Mimicking normal atmospheric microspray conditions (i.e., 1.0 $\mu\text{l}/\text{min}$ flow rate of a solution containing 10 μM each of 3 peptides), we found that the overall detection efficiency of these peptides (1-10 ppb) was at the low end but within experimental error of that routinely observed in normal microspray operation (5-50 ppb). Therefore, the micro/nanospray collection efficiency appears to be near 100%.--

Please replace the paragraph beginning at page 20, line 3, with the following paragraph:

--The NEC proton beam will only provide sufficient ion current below 100 torr because of ion losses to bath gas collisions. This is not a problem for MALDI, which is already conducted at lower pressures, and we have already demonstrated a low pressure ESI head (Figure 4).--

Please replace the paragraph beginning at page 24, line 5, with the following paragraph:

ESI provides the greatest potential for success since the ions can be introduced to the droplet after it leaves the spray tip and before desolvation where solvent separation of the ion pairs may assist us in charge separation before the formation of salt clusters. A low pressure ESI microspray head, ~~similar to that shown in Figure 4~~, can be used with an off-the-shelf TOF analyzer. The head design may be altered by the extension of the spray chamber to allow the introduction of an ion beam or laser perpendicular to the spray direction. In addition, a separate port may be added for the controlled addition of gases through a micro-metering valve to maintain pressure control of the spray chamber. The same test system with minimal modification will serve all subsequent tasks involving ESI.--

Please replace the description of Table 1 beginning at page 10, line 11, with the following:

--Table 1

Total Charges on a Electrospray Drops of Different Sizes
Estimated from Total and Specific Ion Currents (Figure 5).--

Please replace the paragraph beginning at page 24, line 5, with the following paragraph:

--The above evidence suggests that there is a fundamental limit on the ionization efficiency. We believe that this fundamental limit is due to charge separation (i.e., the electroneutrality constraint). If we revisit the issue of droplet formation from the Taylor cone (Figure 5), it is apparent from local electroneutrality constraints that, in the absence of an electric field, every cation must be balanced by a neighboring anion (i.e., all organic ions must be present as salts, albeit solvent separated, in the liquid phase). When the electric field is applied, charge separation in the liquid begins to occur and a local charge imbalance is forced at or near the liquid surface. The degree of charge separation that can occur depends on the magnitude of the applied field. At 10,000 V/cm, dielectric breakdown occurs in air, electron flow from the

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grounded surface to the spray tip begins, and there is a cessation of droplet formation. Therefore, this field strength represents the maximum potential that can be applied for charge separation.--